c) harvesting the culture medium after an incubation period sufficient to allow an accumulation of Adenoviral vector in the culture medium.

CONDITIONAL PETITION FOR EXTENSION OF TIME

If any extension of time for this response is required, Applicants request that this be considered a petition therefore. Please charge the required fee to Deposit Account No. 14-1263.

ADDITIONAL FEES

Please charge any further insufficiency of fees, or credit any excess to Deposit Account No. 14-1263.

REMARKS

Claims 1-6 and 9 are in the application. Claims 1 and 9 have been amended in accordance with several of Examiner's suggestions. New claim 11 has been added.

Claims 1-6 and 9 are objected to based on formal issues. The offending terms have been amended to include hyphens; e.g., "Adenovirus vector producing-cell."

Claims 1-6 and 9 stand rejected under § 112, 1st paragraph for alleged inadequate support in the specification. Specifically, Examiner alleges that the amended claims introduce new matter.

- Claim 1 has been deleted.

- Claim 11 has been added to describe the method wherein the p21 gene and Adenoviral vector DNA can be either linked or unlinked, rather than only unlinked, as in the canceled claim 1. The remarks below explain in detail why the specification clearly provides support for the DNAs being unlinked.

- Claim 9 has been amended to recite a cell that resists apoptosis, rather than prevent apoptosis.

- The remarks below indicate that the alleged lack of support for first and second polynucleotides was indeed supplied in the specification and, was well within the knowledge of persons with skill in the art.

Claims 1-6 and 9 are rejected under § 112, 2nd, paragraph, for allegedly being vague and indefinite. Applicants believe that the following amendments render the rejections moot.

- Claim 1 has been deleted.

- Claim 9 has been amended by adding the noun "cell" to provide for "said Adenoviral vector producing cell."

- The preamble to claim 9 has been amended in accordance with Examiner's suggestions.

Claimed Invention

In reviewing the comments below, Examiner is respectfully reminded of the goal of the claimed method as it is understood by persons of ordinary skill in the gene transfer arts.

The goal of the method is not merely to express p21 as a transgene, but to express p21 in Adenovirus producing cells in order to slow the cells' progression

toward senescence. In this way, Advenoviral vector DNA having one or more distinct transgenes may be amplified and packaged prior to being released into the culture medium. Retarding senescence would maintain the producing cells in a more vigorous state and thus, would prolong the time period for vector production.

The goal of the method is to obtain a preparation of amplified vectors carrying therapeutic and/or diagnostic genes or other DNA sequences of interest. Therefore, persons with ordinary skill would readily appreciate that p21's role in producing the vector is complete after the vector is amplified and produced. Put another way, after the vector is prepared the presence of p21 DNA in the diagnostic/therapeutic Adenoviral vector is completely superfluous. Thus, persons with ordinary skill would not limit this method to one where the p21 DNA is linked with the diagnostic/therapeutic vector. One would only require such a vector if *one wanted to study the in vivo behavior or effects of p21 expression itself.* This is not remotely related to the subject matter of the claims

It follows from this that it would be whether a p21 gene was physically linked, i.e., on the same fragment, as the Adenoviral DNA vector to be amplified.

Further, the size of the amplified genome that can be packaged into the budding Adenoviral viral vector has an upper size limit (~ 35 kb). Therefore, it is often not preferred to link an nontherapeutic/nondiagnostic gene (i.e., p21) on the produced vector DNA because it takes up valuable space that is preferably reserved for cloning of additional diagnostic and therapeutic genes.

Therefore, in practicing the claimed method, one with skill in the art would almost always be inclined to have the p21 cassette on a different DNA fragment from that of the Adenoviral DNA. In other words, it would be clear to those in the art without any additional guidance or evidence that the method encompasses embodiments wherein the p21 and Adenoviral DNA are unlinked.

As discussed below, the specification, including the original claims, clearly provide support for embodiments comprising an unlinked p21 gene cassette and Adenoviral vector DNA. In other words, there was adequate support for such claims.

In addition, it is also discussed below in more detail why persons with skill in the art would clearly appreciate that the disclosed method encompasses two genes being on either the same or different DNA fragments.

Applicants respectfully suggest that the rejection based on alleged inadequate support in the specification should be withdrawn.

Written Description and New Matter

In general, "an issue of new matter will arise if the content of the amendment is not described in the application as filed." MPEP § 2163.06. Thus, the assessment of new matter is virtually identical to determining whether or not original claims satisfy the written description requirement. *Id.* "Information contained in any one of the specification, claims, or drawings as filed" is available to assess an amended claim's content. *Id.*

"[T]he 'essential goal' of the description of the invention requirement is to clearly convey the information that an applicant has invented the subject matter which is claimed." *In re Barker*, 194 USPQ 470, 473 n.4 (CCPA 1977). Another objective is to put the public in possession of what the applicant claims as the invention. See *Regents of the University of California v. Eli Lilly*, 43 USPQ2d 1398, 1404 (Fed. Cir. 1997).

Applicants suggest that they have fulfilled this requirement because the information, guidance or description that Examiner apparently requires [i] was disclosed in the specification and claims as filed, and [ii] has been well-known in the art since the late 1970s to early 1980s, when the pioneering work of Axel and Wigler et al., showed that transfecting cells with unlinked DNAs (i.e., on different plasmids)

or linked DNAs together on the same plasmid or fragment, made little difference in obtaining the desired colonies transfected colonies. Thus, early in the development of the gene transfer field, skilled artisans were aware of this duality of achieving similar results.

Respectfully, it is improper to ignore these principles as well as the vast body of knowledge that evolved from them. For the following reasons, one with ordinary skill in the art would clearly have understood that the invention as claimed was in Applicants' possession.

The thrust of the rejection is that the specification does not support a method wherein the p21 gene and the Ad vector to be replicated, are co-transfected into vector producing cells are on separate, unlinked DNAs. In Examiner's view, one with skill in the art would read the specification to suggest **only** the production of Adenoviral vectors having a p21 gene. This is certainly not correct.

Original Specification Provides Adequate Support

Applicants respectfully remind Examiner that the claims as filed in the original specification are part of the disclosure and, therefore, if an application as originally filed contains a claim disclosing material not found in the remainder of the specification, the applicant may amend the specification to include the claimed subject matter. *In re Benno*, 226 USPQ 683 (Fed. Cir. 1985).

The instant amended claims merely include disclosed material that has been re-worded for more clarity and to reflect more proper English. However, the amended claims are clearly supported in the specification and do not represent new matter.

The following references disclose p21 and Ad DNA being on physically separate DNA molecules when introduced into cells:

1. **Specification, page 3, 2nd paragraph** states that p21 may be transferred as "naked DNA" or as "DNA packaged into vectors which can be of viral or non-viral nature."
   This sentence expressly discloses an embodiment of the method whereby p21 is expressed in a non-viral vector. Accordingly, it is indisputable that expressing p21 in a non-viral vector precludes p21 DNA from being linked to Adenoviral DNA as part of the Ad-vector to be amplified. In other words, in this embodiment, the p21 and the Adenoviral vector DNA must be unlinked.
   On this basis alone, the examiner could properly withdraw the new matter rejection.

2. **Original claim 6** specifies that the p21 may be used in viral OR *non-viral vectors*. Expressing p21 from a non-viral vector requires that p21 not be linked to Ad-vector DNA. This provides support for the amended claims.

3. **Specification, page 2, text line 5,** reads, "Overexpression of p21 prevents apoptosis of the cells ***after*** infection with the Ad vector to be amplified and improves culture medium conditions."
   Thus, it is clearly disclosed that Applicants contemplate overexpressing p21 ***before*** infecting with the Ad vector DNA. The earlier p21 expression "prepares" the cells to fight off the Adenovirus-induced senescence. This can best accomplished if the p21 and Ad vector DNA are physically unlinked, as covered in new claim 11. When unlinked, the skilled artisan has complete control over determining (and optimizing) the lag period between p21 expression and Ad vector infection.

4. **Original claim 8** describes an embodiment where the p21 is stably introduced into the production cell line. Thus, to carry out the method of producing Adenoviral vectors, the Adenoviral vector DNA must be transfected at a later time – this can only be performed if the DNAs are physically separate.
   Person with ordinary skill would understand this because one cannot stably transfect a production cell line with Adenoviral vector DNA because the Adenoviral vector DNA eventually results in lytic infection which kills the cells. No stable transformants could be obtained with the Ad-vector DNA, thus the p21 and Ad-vector DNA must be separated.

5. **Original claim 5** discloses p21 expression from a regulated promoter. It is known in the art that Adenoviral vectors have no regulated promoters. Thus, it is clear that the p21 gene was contemplated to be expressed in a context of non-Adenoviral DNA – that is, on a fragment physically separate from the Ad-vector.

6. **Specification, page 3, 5th paragraph** refers to the produced Ad vector as being harvested at an optimal time – there is no reference to the harvested Ad vectors having p21. It is suggested that Examiner has improperly read into this text that the produced viral vector must also have the p21 gene.

7. **Specification, page 3, 6th and 7th paragraphs** refer to "different Ad" vectors and different encoded transgenes, none of which are referred to as possessing, requiring, or actually being, p21. This discloses the versatility of the method is disclosed **without any express or implied limitations suggesting that p21 be physically linked to the Adenoviral vector to be produced.**
   One with skill in the art would clearly appreciate that includes p21 and Adenovirus vector DNA being physically unlinked. It is against PTO

guidelines and federal case law to ignore this understanding to reach Examiner's improperly narrow interpretation.

Applicants suggest that there is ample disclosure that would inform those with ordinary skill in the art that that the claimed methods contemplate both linked or unlinked DNAs encoding p21 and Adenoviral vector sequences.

In fact, it is respectfully suggested that there is no disclosure suggesting that the claimed method is exclusively directed to using linked DNA.

In light of the foregoing remarks, Applicants respectfully suggest that Examiner has given too much weight to the fact that the exemplified embodiments demonstrate p21 linked to Adenoviral sequences.

The Claims are Enabled

In view of the state of the art and the level of skill, Applicants point out that the claims are enabled by the specification because one with ordinary skill could fully practice the claimed method without undue experimentation. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir.1988).

"The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." *United States v. Telectronics, Inc.*, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988).

As described above, it has been long understood in the art that two genes can be co-transfected while physically linked on the same vector or unlinked on distinct vectors. The same recombinant methodology provides for, e.g., p21 linked with Adenoviral vector DNA or unlinked DNA so it may be expressed from an inducible or non-viral promoters.

In sum, "[a] patent need not teach, and preferably omits, what is well known in the art." *In re Buchner*, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). Essentially any method for amplifying Adenoviral vector DNA in a p21-expressing production line, inherently provides persons in the art the choice of expressing p21 and Adenoviral DNA comprising additional transgenes, from either the same or distinct DNA fragments. This is so well known in the gene transfer and vector construction arts that persons of ordinary skill would not need any extrinsic guidance to perform these variations of the method based on Applicants' disclosure.

In view of this widespread understanding, and the text cited herein, Examiner would be justified in withdrawing the rejection under § 112, 1st¶.

Applicants respectfully request that the rejection be withdrawn because the apparent attempt to narrow the claims to a single embodiment is inappropriate.

Respectfully Submitted,

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MARK UP OF AMENDED CLAIMS

2. (Amended five times) The method of claim 11 ~~1~~ comprising utilizing a constitutive promoter operatively coupled to the nucleotide sequence encoding p21 for the generation of stably transfected cell lines.

3. (Amended four times) The method of claim 11 ~~1~~ comprising utilizing a regulatable promoter operatively coupled to the nucleotide sequence encoding p21 for the generation of stably transfected cell lines.

4. (Amended four times) The method of claim 11 ~~1~~ comprising utilizing a constitutive promoter operatively coupled to the nucleotide sequence encoding p21 for the generation of transiently transfected cell lines.

5. (Amended four times) The method of claim 11 ~~1~~ comprising utilizing a regulatable promoter operatively coupled to the nucleotide sequence encoding p21 for the generation of transiently transfected cell lines.

6. (Amended four times) The method of claim 11 ~~1~~ wherein the transfer of the nucleotide sequence encoding p21 is carried out using known transfer techniques employing naked DNA or viral or nonviral vectors.

9. (Amended twice) A method for ~~preventing~~ preparing a an Adenovirus vector-producing cell that resists apoptosis during Adenovirus vector amplification ~~in an Adenovirus vector-producing cell,~~ comprising:

a) ~~introducing~~ contacting a polynucleotide ~~nucleotide~~ sequence encoding p21 ~~into~~ with an Adenoviral vector-producing cell simultaneously with, or followed by,

b) ~~introducing~~ contacting a polynucleotide sequence comprising an ~~the~~ Adenoviral vector to be amplified with ~~into~~ said Adenoviral vector-producing cell, and

c) generating a transfected cell which resists apoptosis during adenoviral vector amplification, and wherein said p21 nucleotide sequence is operatively coupled to a ~~constitutive or regulatable~~ viral or non-viral promoter.